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(54) Title: PROCESS FOR THE MANUFACTURE OF (SUB)MICRON SIZED PARTICLES BY DISSOLVING IN COMPRESSED GAS AND SURFACTANTS

(57) Abstract

The present invention relates to a process for manufacturing a pulverous preparation of a (sub)micron-sized biologically active compound comprising the steps of: (1) dissolving a biologically active compound under elevated pressure in a compressed gas, liquid or supercritical fluid containing a surface modifier; or in compressed dimethylether optionally containing a surface modifier; (2a) rapidly expanding the compressed solution of step (1) thereby precipitating the dissolved compound; or (2b) spraying the compressed solution of step (1) into an antisolvant phase optionally containing a surface modifier under vacuum, atmospheric pressure or elevated pressure; and (3) optionally converting the antisolvant phase of step (2b) into a pulverous preparation using conventional powder processing techniques. With the process according to the present invention formation of aggregations or flocculations of particles dissolved in the supercritical solution is prevented; moreover, the addition of cosolvents is not required, thus increasing the stabilisation of the suspension on an industrial scale.

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Process for the manufacture of (sub)micron sized particles by dissolving in compressed gas and surfactants

The invention provides a novel process for producing (sub)micron-sized particles of a biologically active compound (pharmaceutical).

In the last years a number of different processes to produce very small particles of a pharmaceutical have been described. (e.g. RESS,GAS,PGSS, SAS). These processes are e.g. described in Journal of Pharmaceutical Sciences Vol. 86, No. 8, August 1997, pp. 885-890 under the title "Pharmaceutical Processing with Supercritical Carbon Dioxide. Thereby the drug is dissolved in a compressed gas and subsequently rapidly expanded mostly into atmospheric pressure. Due to the expansion conditions and to a high surface energy in the gas very small particle sizes (smaller 1 µm) are hard to achieve and to handle. Such high surface areas can only be handled by using a surface modifier to decrease the surface energy. This fact is well known for a long time and used for stabilization of small particles in suspension. (H. Sucker, P. Fuchs, P. Speiser, "Pharmazeutische Technologie", 2. Edition, 1991, Georg Thieme Verlag, Stuttgart/New York, pp 419-424; and Hans Steffen, BT Gattefossé No. 81, 1988, pp. 45-53, "Controlled Precipitation- a Method to Produce Small Drug Particles and to Increase Bioavaibility".)

The International application WO 97/14407 describes a supercritical fluid/compressed fluid based process to produce submicron-sized particles of biologically active compounds which process comprises the steps of:

(1) dissolving a water insoluble biologically active compound in a solvent thereof;

(2) spraying the solution of step (1) into a compressed gas, liquid or supercritical fluid in the presence of a surface modifier dispersed in an aqueous phase.

In another embodiment the process described in WO 97/14407 is carried out comprising the steps of:

(1) dissolving a water insoluble biologically active compound in a compressed fluid;

(2) spraying the compressed fluid of step (1) into an aqueous phase containing a surface modifier.

The process described in WO 97/14407 may be difficult to realize on an industrial scale for the following reasons:

- On an industrial scale it is difficult to reach a uniform distribution of temperature in the connection tubes. Due to such variations in temperature aggregation or flocculation of particles dissolved in the supercritical solution might occur causing clogging of the tubes or spraying-nozzles.

- The solubility of most of the pharmaceutical compounds in liquid or supercritical CO_2 is very low even under high pressure. Therefore the use of additional cosolvents is proposed. Most of these cosolvents are liquids under atmospheric pressure.By spraying the solution containing the pharmaceutical into the liquid phase (e.g. aqueous phase) the fraction of the cosolvent in the liquid phase increases. Therefore the solubility of the compound in the liquid phase also increases. This can destabilize the suspension on an industrial scale.

- In addition, the recycling of the pressurized gas becomes more difficult and expensive using a cosolvent.

A pressurized gas with high solubility for most of the pharmaceutical compounds would allow the process to be effected without the use of cosolvents.

The object of the present invention is thus to provide a novel process for producing (sub)micron-sized particles of a biologically active compound (pharmaceutical) from a compressed gas, liquid or supercritical fluid avoiding the above mentioned difficulties.

The process of the present invention is based on the use of compressed gas and fluids including supercritical technology yielding (sub)micron-sized particles having a narrow size distribution and being stabilized by a surface modifier.

The suggested process can be performed either batchwise or continuously and is applicable to a wide range of substances.

In a first aspect of the invention it has now been found that the above mentioned problems concerning the cosolvent can be avoided by using compressed dimethylether to solve the biologically active compound

In a second aspect of the invention it has now been found that the above mentiond problems of clogging can be avoided by stabilizing the supercritical solution by adding a surface modifier in the compressed gas solution.

The invention thus concerns a process for the manufacture of a pulverous preparation of a (sub)micron-sized biologically active compound comprising the steps of:

(1) dissolving a biologically active compound under elevated pressure in a compressed gas, liquid or supercritical fluid containing a surface modifier; or in compressed dimethylether optionally containing a surface modifier;

(2a) rapidly expanding the compressed solution of step (1) thereby precipitating the dissolved compound; or

(2b) spraying the compressed solution of step (1) into an antisolvant phase optionally containing a surface modifier under vaccuum, atmospheric pressure or elevated pressure;

(3) optionally converting the antisolvant phase of step (2b) into a pulverous preparation using conventional powder processing techniques.

Convential powder techniques are for example spray drying and freeze drying.

In this manner the formation of (sub)micron sized particles stabilized by a surface modifier is achieved.

The term "(sub)micron-sized particles" embraces particles having a medium diameter (Dv 0.5) of 5nm to 5µm, preferably 200nm to 1 µm.

In cases where the compressed fluid is compressed dimethylether, the use of surface modifier is optionally and can be added to the compressed fluid (step 1) or to the antisolvant phase.

However, in all the other cases where the compressed fluid is not dimethylether, a surface modifier must be added to the compressed fluid.

The term “surface modifier” in step (1) and step (2b) of the present process embraces common modifiers as described in “Pharmazeutische Technologie, 4. Edition, 1993, Georg Thieme Verlag Stuttgart, New York.”

Examples of suitable modifiers are:

- natural surfactants such as e.g. gelatine, paraffin, cholesterol esters and triglycerides;
non-ionic surfactants such as e.g. polyethylene glycol;
- anionic surfactants such as e.g.natrium dodecylsulfate
- cationic surfactants such as e.g.quaternary ammonium compounds;
- block copolymers of ethylene oxide and propylene oxide available from BASF under the trade name Pluronic®;
- polyoxamines availaible under the tradename Tetronic ®;
- polyoxyethylen sorbian fatty acid esters, e.g. Tween 20, 40, 60 and 80.
- Klucel EF,
- Eudragit E,
- Arlactel 40,
- Carbopol 940,
- PVP K50;
- Brij 96 and Aerosol OT®.

Preferred surface modifiers are Brij 96® (polyethylenglykolether of lauryl,-cetyl-, stearyl- and oleylalcohols, available from Atlas Chemie) and Aerosol OT® (sodium di-isooctylsulphosuccinate availaible from Wako Junyaku Corp).

In step (1) and step (2b) of the process the same modifier can be used.

As shown by H. Steffen (BT Gattefossé No. 81, 1988, pp. 45-53,) the concentration of the surface modifier depends on the critical micelle concentration (CMC). The amount of surface modifier needed depends therefore on the CMC and the surface aerea of the particles.

The addition of a surface modifier to the compressed gas prior to the spraying has the advantage that

(i) nuclei and particles formed spontaneously in the pipes or - due to the pressure drop - in the region of the nozzle are immediately stabilized and their growth is hindered further, thereby preventing clogging,

(ii) the mixing of the precipitated particles and the surface modifier is improved by simultaneously spraying the solution of the drug and the surface modifier through the same nozzle,

(iii) the use of an antisolvent phase which neither solubilizes the drug nor the surface modifier is allowed.

Due to the presence of a surface modifier in the compressed gas, liquid or supercritical liquid the following advantages are achieved:

- Differences of the pressure and temperature are counteracted by stabilizing any nuclei formed.
- The pressure drop in the region of the nozzle can be accommadated without clogging.
- The surface modifier is located very close to the region of particle formation and not distributed in the whole liquid.
- It is possible to expand into a liquid phase (e.g. compressed CO_2), which is then evaporated by keeping the stabilization of the suspension. Thus, the additional step of spray drying is no longer necessary.

The term "compressed gas, liquid or supercritical fluid" embraces dimethylether, carbon dioxide, straight chain or branched C1-C6- alkanes or combinations thereof. Examples for said alkanes are e.g.ethane, propane, butane and isopropane and the like.

The term "biologically active compound" includes e.g.pharmaceuticals as listed below:

therapeutic category	INN (international non-proprietary name)
anxiolytic	Diazepam, Bromazepam
antidepressant	Moclobemide
anesthetic	Midazolam
antiviral	Ganciclovir, Zalcitabine, Nelfinavir mesylate
proteinase inhibitor	Saquinavir, Nelfinavir
anti-inflammatory	Naproxen, Tenoxicam, Ketorolac
antibacterial	Ceftriaxone, Timethoprim, Sulfamethoxazol.
antimalarial	Mefloquine
antihypertensive	Cilazapril
antiseborrheic	Isotretinoin
calcium regulator	Calcitriol
lipase inhibitor	Orlistat
antiparkinson	Tolcapone
antiarthritic	Mycophenolate mofetil
antithrombotic	Lamifiban
endothelin antagonist	Bosentan

The antisolvant can be any solvent wherein the pharmaceutical is poorly soluble. For example the antisolvant can be water or compressed CO_2

The temperature in steps (1) or (2b) is each independently in the range of 0-250°C, preferably 20-60°C.

The pressure in step (1) is $2\text{-}500 \times 10^5$ Pa, preferably $2\text{-}300 \times 10^5$ Pa and the pressure in step (2b) is $0.05\text{-}500 \times 10^5$ Pa, preferably $1\text{-}200 \times 10^5$ Pa, most preferably $3\text{-}100 \times 10^5$ Pa.

Preferably the pressure in step (1) and step (2b) is not the same. The pressure difference is used to control the particle size.

The invention is further explained with reference to the attached drawings in which

- Fig. 1 is a schematic representation of an apparatus for carrying out the present invention;
- Fig 2 and Fig.3 show the particle size distribution of the same suspension but using different methods to determine the particle size distribution.

Fig. 2 shows the particle size distribution of Saquinavir using Photon Correlation Spectroscopy (batch no. 1051/30) ; Rec 7; Angle 90; KCps 931.3; ZAve 254.7; Poly 0.031; Multi Angle.

Fig. 3 shows particle size distribution of Saquinavir using Laser Diffraction (batch no. 1051/30); modifier Aerosol OT; dimethylether; focus 50mm;

Fig. 1 is described as follows:

A 6 l high pressure vessel (3) for dissolving the drug substance (and optionally the surface modifier) was connected via an outlet tube to a 4 l high pressure vessel (8) which was used as the precipitation unit. The dissolution unit (3) was equipped with a container (4) closed with two sinter plates (5) which retained the solid drug substance (and if present the solid surface modifier) but allowed free flow of the compressed fluid and drug (and optionally surface modifier) / compress fluid solution through it. A bypass line (1) allowed to pre-pressurize the precipitation unit (8). The temperature of the two vessels (3) and (8) was controlled independently of each other by two thermostates TC1 and TC2. All pipes were heated by heating tape. The pressure in the two vessels (3, 8) was controlled using two pressure regulators

(7, 10). The flow rate through the nozzle (9) was measured with a flow meter (11). The expansion nozzle included a 1.5 mm thick, 0.1mm diameter laser drilled orifice. The downstream end of the orifice was counterbored into a V-shape.

A typical experiment consisted of:

(i) charging the container (4) with the desired amount of drug substance and (optionally) surface modifier,

(ii) closing the container with the sinter plates (5) and putting it into vessel,

(iii) adding the antisolvent (optionally together with surface modifier) to the precipitation unit (8),

(iv) pressureizing the two vessels (3) and (8) on the desired pressure levels, and

(v) thermostating the vessels and the pipes on the desired temperature levels.

The whole system was equilibrated (e.g. 90 min), after which the spraying process was started by pumping additional compressed fluid into vessel (3). The increase of the pressure in the dissolution chamber (3) forced the pressure regulator (7) to open the valve to the spraying unit thereby starting the spraying. The differential pressure between the first (3) and second (8) vessel was controlled by a pressure regulator (10). The flow rate through the nozzle (9) was controlled by adjusting the pump flow rate (2). During the whole experiment, temperature and pressure in the two vessels (3, 8) were monitored constantly.

A continuous process can be achieved by continuous, controlled feeding of drug substance (and optionally surface modifier) into the dissolution unit (3), dissolving it in the compressed fluid and spraying the solution into the antisolvent phase in the precipitation unit (8). Suspension is continually removed from the precipiation unit and replaced by new antisolvent (optionally containing surface modifier).

The particle size distribution of very small particles of approximately 1 µm is very difficult to determine accurately. In principle there are two different methods commonly used, photon correlation spectroscopy (PCS) and laser diffraction. Photon correlation spectroscopy is commonly used for

characterization of submicron suspensions and emulsions. Due to the principle of the measurement (movement of particles) particles larger than 3 to 5 µm cannot be seen with this method. With laser diffraction small particles (>0.1 µm) as well as larger particles (up to 2 mm) can be characterized in parallel. The diffraction of the light is thereby measured at small diffraction angles. For very small particles the method tends to overestimate the particle size due to transition of light through the particles. This effect of over- and underestimation of the particle size by the two methods is demonstrated in Figure 2 and Figure 3, showing the particle size distribution of the same suspension, measured with PCS (Figure 2), and with laser diffraction (Figure 3).

To assess the performance of a process for the formation of (sub)micron-sized particles, it is important to show that - besides the fine partilces - no fractions of large particles are formed. Formation of fractions of coarse particles was observed especially after clogging of the nozzle (e.g. expansion of a compound dissolved in a compressed gas without modifier). To be able to detect the presence of coarse particles, laser diffraction was chosen to characterize the whole suspension. With its wide dynamic range, laser diffraction allowes the detection of particles up to 2 mm that cannot be seen by the PCS method. Since laser diffraction tends to overestimate the particle size (Figures 2, 3), all the particle sizes determined by laser diffraction can be considered as too large. Nevertheless laser diffraction proved to be sensitive enough to show the influence of different process parameters on the particle size.

The following Examples explain the invention in more detail.

<u>Example 1:</u>. Solubilities of pharmaceutical drug substances in liquid carbon dioxide and dimethyl ether

A comparison of solubilities of a number of pharmaceutical drug substances was performed as follows:

App. 3-5 g of the drug product was slightly compressed in an uniaxial press to avoid the formation of a stable suspension. The so compressed powder was given in a pressure chamber with a sapphire glass (30 ml volume). The temperature of the pressure chamber was controlled by water bath. Then the pressure in the chamber was increased using the corresponding gas and

equilibrated for 1-3 hours. After equilibration a defined sample (1.0 ml) was drawn under constant pressure and temperature conditions using a high pressure line with a defined volume. This sample was expanded into a liquid with a good solubility for the respective compound. The sample container was afterwards rinsed with the same liquid to collect the residues of the substance in the sample container.

The solubility (G/V) was determined either by HPLC or gravimetrically after removing the liquid.

Solubilities of pharmaceutical drug substances in liquid carbon dioxide and dimethyl ether

drug substance	solubility (CO_2) [%(g/V)]	conditions [°C/bar]	solubility (DME) [%(g/V)]	conditions [°C/bar]
Orlistat (THL)	0.6	30°C/100 bar	17.8	20°C /4.5 bar
Isotretionin	0.3	45°C/200 bar	6.0	45/200 bar
Sulfamethoxazol	0.1	45°C/140 bar	5.4	45°C/140 bar
Saquinavir	< 0.1	45°/200 bar	> 10	25°C/100 bar
Diazepam	0.15	45°C/200 bar	> 10	45°C/200 bar
Moclobemide	0.35	45°/200 bar	3.7	45°C/200 bar
Bosentan	< 0.1	45°C/200 bar	9.0	45°C/200 bar

Example 2: Expansion of Orlistat (Tetrahydrolipstatin THL) - Influence of the spraying time

150 g of solid THL and 75 g Brij 96 in a container with two sinter plates was charged into an autoclave having a volume of 6 l. The autoclave was kept at a temperature of 40°C with a water bath. Then the autoclave was filled with CO_2 up to a pressure of 200 bar and equilibrated for 90 min.

The autoclave was connected to a second autoclave via a heated high pressure line, kept at 40°C. This second autoclave had a volume of 4 l. The dissolved THL was sprayed into a 1.25l of an aqueous solution (0.06% =1 CMC) this second autoclave. Thereby the pressure of the first autoclave was kept constant at 200 bar by pumping in additional gas.

(Several trials spraying a solution of THL in CO_2 without surfactant into an aqueous solution with various concentrations of Brij 96 was not successful due to clogging of the nozzle. The small amount of surfactant (1 CMC) was not added for stabilization.).

After 90,150 , and 180 min spraying a sample for particle size distribution was drawn. After 180 min the whole amount of THL/Brij was removed from the first container (≈ 12%THL in the final suspension). That means that a solid concentration of 5-8 % should be achievable in production scale.

As listed below the resulting particle size distribution of THL was kept almost constant over the whole trial (see table below). This shows that stabilization of the nuclei with the surfactant was very effective up to a high solid concentration. This fact is a prerequisite for a effective process.

Particle size distributions determined with laser diffraction .

Spraying Time	Dv 0.1 [μm]	**Dv 0.5 [μm]**	Dv 0.9 [μm]
90 min	0.6	**1.4**	2.9
150	0.4	**1.5**	3.5
180	0.9	**2.1**	4.5

<u>Example 3:</u> Expansion of Saquinavir - Influence of the pressure in the first container on the resulting particle size

50 g of solid Saquinavir and 25 g Aerosol OT in a container with two sinter plates was charged into an autoclave having a volume of 6 l. The autoclave was kept at a temperature of 40°C with a water bath. Then the autoclave was filled with DME up to different pressures and equilibrated for 90 min.

The autoclave was connected to a second autoclave via a heated high pressure line, kept at 25°C, 5 bar. This second autoclave had a volume of 4 l. The dissolved Saquinavir/Aerosol OT was sprayed into a second autoclave filled with 1.2l of pure water. Thereby the pressure of the first autoclave was kept constant by pumping in additional gas.

(Several trials spraying a solution of Saquinavir in DME without surfactant into an aqueous solution with various concentrations of surfactant was not successful due to clogging of the nozzle)

After 20 min spraying a sample for particle size distribution was drawn. (≈ 4% Saquinavir in the final suspension).

The resulting particle size distribution of Saquinavir could be controlled by the pressure applied in the first container (see table below). This shows that as theoretically proposed the supersaturation can be kept very constant during the process and correlates with the resulting particle size. Also the stabilization of the nuclei with the surfactant was very effective. This fact is also a prerequisite for a effective and controlled process.

The nozzle diameter was 0.1 mm. As commonly known a further decrease of particle size can be obtained by decrease of the nozzle diameter.

Particle size distributions determined with laser diffraction .

Pressure	Dv 0.1 [µm]	**Dv 0.5 [µm]**	Dv 0.9 [µm]
50 bar	0.5	**3.8**	6.4
100 bar	1.0	**2.1**	4.5
200 bar	0.9	**1.5**	2.4

280 bar	0.4	**0.8**	1.7

Example 4: Expansion of Saquinavir - Influence of the surfactant

50 g of solid Saquinavir and 5 g Brij 96 in a container with two sinter plates was charged into an autoclave having a volume of 6 l. The autoclave was kept at a temperature of 40°C with a water bath. Then the autoclave was filled with DME up to 200 bar and equilibrated for 90 min.

The autoclave was connected to a second autoclave via a heated high pressure line, kept at 25°C, at 5 bar. This second autoclave had a volume of 4 l. The dissolved Saquinavir/Brij 96 was sprayed into a second autoclave filled with 1.2l of pure water. Thereby the pressure of the first autoclave was kept constant by pumping in additional gas.

After 20 min spraying a sample for particle size distribution was drawn. (≈ 4% Saquinavir in the final suspension).

The resulting particle size distribution of Saquinavir stabilized with Brij 96 (not ionic surfactant) was comparable with the results obtained with Aerosol OT (ionic surfactant, see Example 3).

Particle size distributions determined with laser diffraction .

Surfactant	Dv 0.1 [µm]	**Dv 0.5 [µm]**	Dv 0.9 [µm]
Aerosol OT	0.9	**1.5**	2.4
Brij 96	0.7	**1.4**	3.0

Claims

1. A process for the manufacture of a pulverous preparation of a (sub)micron-sized biologically active compound comprising the steps of:

(1) dissolving a biologically active compound under elevated pressure in a compressed gas, liquid or supercritical fluid containing a surface modifier; or in compressed dimethylether optionally containing a surface modifier;

(2a) rapidly expanding the compressed solution of step (1) thereby precipitating the dissolved compound; or

(2b) spraying the compressed solution of step (1) into an antisolvant phase optionally containing a surface modifier under vaccuum, atmospheric pressure or elevated pressure;

(3) optionally converting the antisolvant phase of step (2b) into a pulverous preparation using conventional powder processing techniques.

2. A process according to claim 1, wherein the compressed gas is carbon dioxide.

3. A process according to claim 1, wherein compressed dimethylether is used to dissolve a biologically active compound (step 1).

4. A process according to any one of claims 1-3, wherein the temperature in step (1) or (2b) is each independently in the range of 0-250°C, preferably 20-60°C.

5. A process according to any one of claims 1-4, wherein the pressure in step (1) is 2-500x10^5 Pa, preferably 2-300x10^5 Pa and the pressure in step (2b) is 0.05-500x10^5 Pa, preferably 1-200x 10^5 Pa, most preferably 3-100x10^5 Pa.

6. A process according to claim 5, wherein a pressure difference exists between step (1) and step (2), said pressure difference being used to control the particle size.

7. A process according to any one of claims 1-6, wherein the surface modifier is a polyethylenglykolether of lauryl,-cetyl-, stearyl- and oleylalcohols or sodium di-isooctylsulphosuccinate.

8. A process according to any one of claims 1-7, wherein the particles have a medium diameter (Dv 0.5) of 5nm to 5µm, preferably 200nm to 1 µm.

9. A process according to any one of claims 1-8, wherein the biologically active compound is a proteinase inhibitor, lipase inhibitor, an antiseborrheic compound, an antibacterial compound, an anxiolytic compound, an antidepressant compound or an endothelin antagonist.

10. A process according to claim 9, wherein said proteinase inhibitor is Saquinavir; said lipase inhibitor is Orlistat; said antiseborrheic compound is Isotretinoin; said antibacterial compound is Sulfamethoxazol; said anxiolytic compound is Diazepam; said antidepressant compound is Moclobemide; and said endothelin antagonist is Bosentan.

11. A process according to any one of claims 1-10, wherein the antisolvant phase is water or compressed CO_2.

12. A process according to any one of claims 1-11, wherein the antisolvant phase is compressed CO_2 and the pulverous preparation is obtained by evaporating the antisolvant phase to atmospheric pressure.

13. A process according to any one of claims1-12, wherein the process is performed batchwise.

14. A process according to any one of claims1-11, wherein the process is performed continuously comprising the steps of:
(1) controlled feeding of a biologically active compound and optionally a surface modifier into the dissolution unit;
(2) dissolving said biologically active compound in the compressed fluid and spraying the solution into the antisolvent phase in the precipitation unit;
(3) continually removing the suspension from the precipiation unit and replacing the suspension by new antisolvent optionally containing surface modifier.

15. Pharmaceutical preparation obtainable using a process according to any one of claims 1-14.

***

Fig. 1

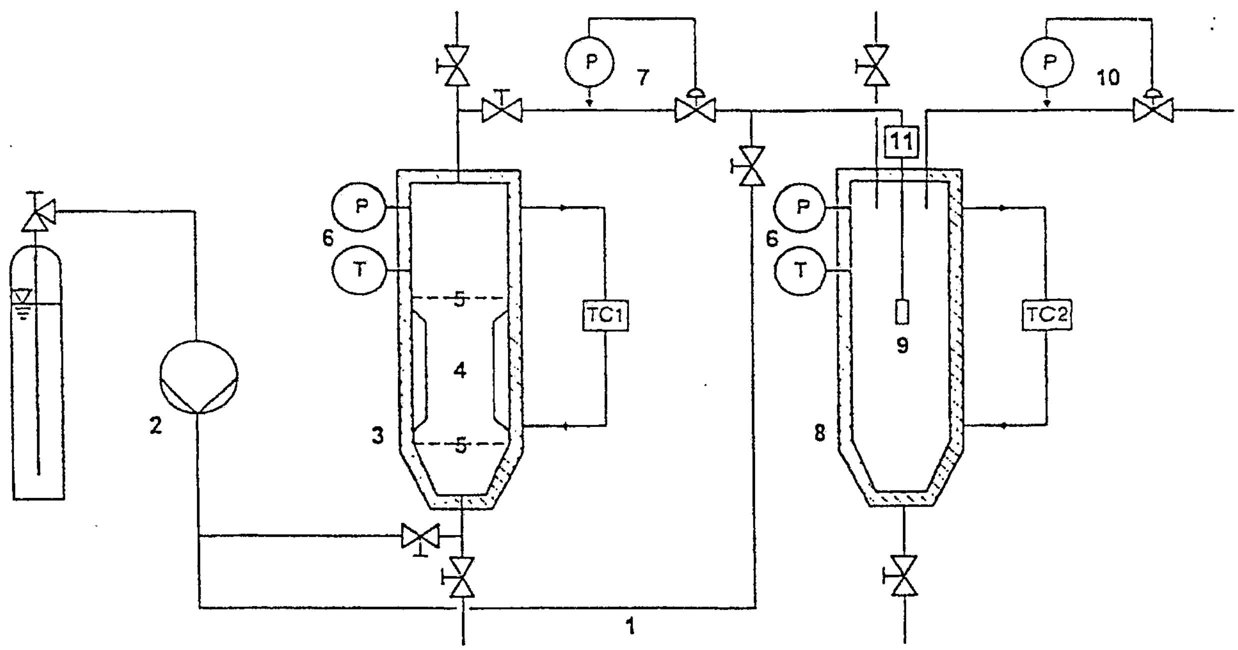
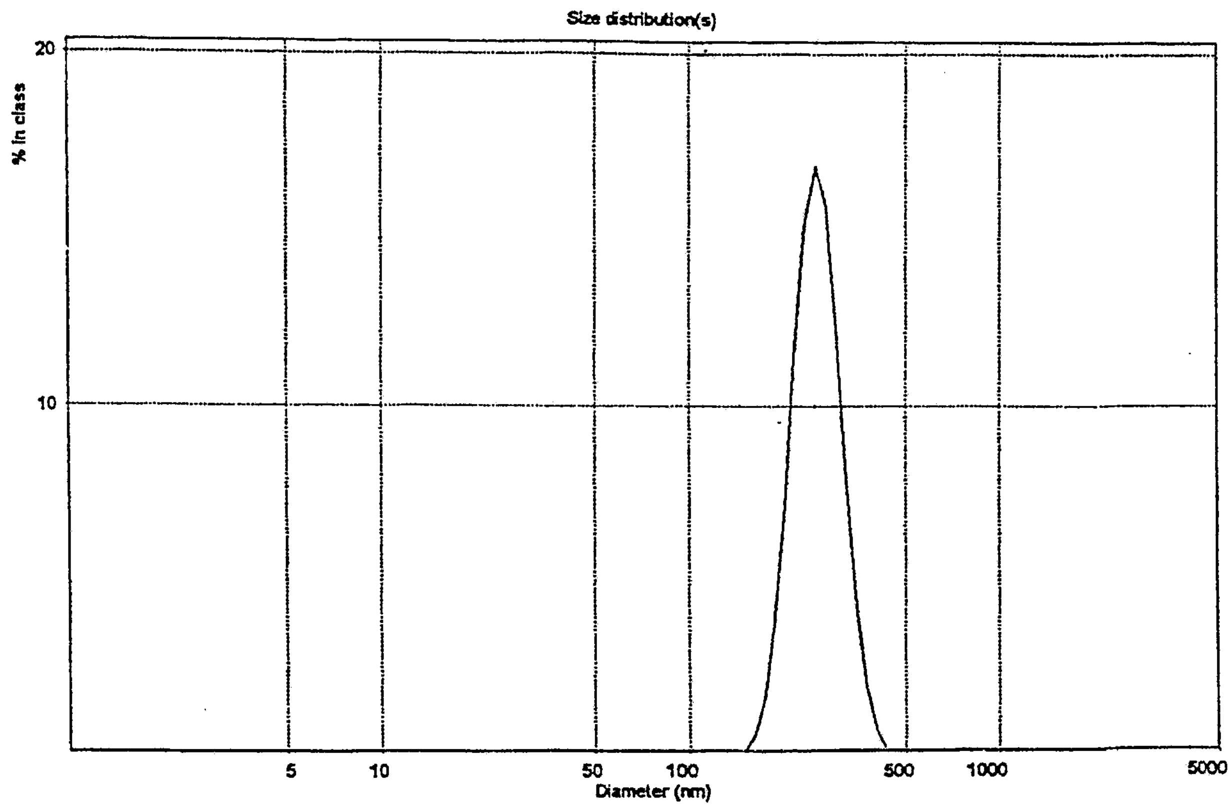


Fig. 2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% in class
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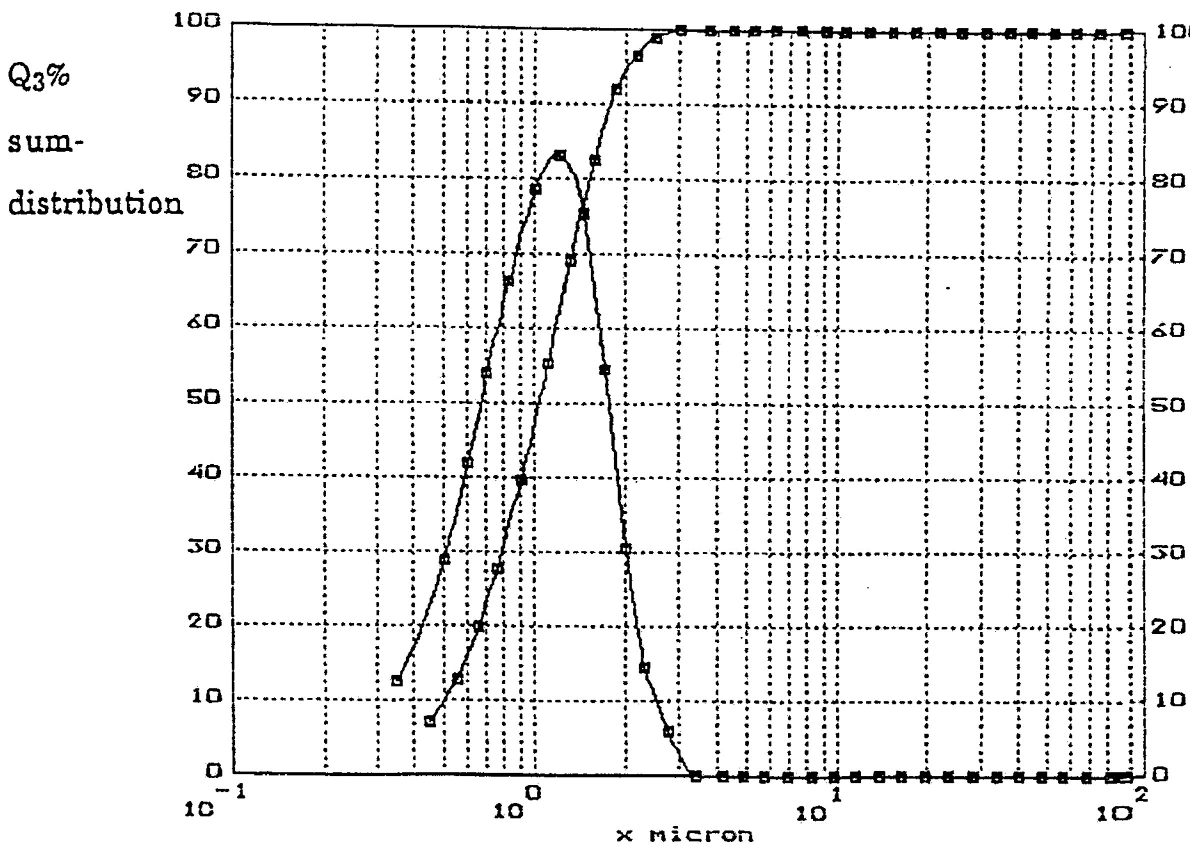
10
50
100
500
1000
5000
Diameter (nm)

Fig. 3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sum-
distribution
100
90
80
70
60
50
40
30
20
10
0
10^-1
10^0
10^1
10^2
x micron

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/02316

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/14 A61K31/015 C08J3/12 B01J2/00 B01J2/04
B01J13/00 B01F3/00 B29B9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C08J B01J B01F B29B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 14407 A (RESEARCH TRIANGLE PHARMACEUTICALS) 24 April 1997 (1997-04-24) page 4, paragraph 2; claims; examples ---	1,2,4,5, 7-13,15
X,P	WO 98 16204 A (F. HOFFMANN-LA ROCHE AG) 23 April 1998 (1998-04-23) page 9, line 10 - line 14; claims ---	1-10, 13-15
X	US 4 734 227 A (SMITH, R.D.) 29 March 1988 (1988-03-29) abstract column 3, line 23 - line 42; figure 8; table 1 ---	1,2,4-6, 8,13
Y	WO 95 21688 A (WEIDNER, E.) 17 August 1995 (1995-08-17) claims; table 2 ---	1,2,4-6, 8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 1999	27.09.1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2	

INTERNATIONAL SEARCH REPORT

Interr nal Application No
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